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<u>L9</u>	L7 and (nails)	2	<u>L9</u>
<u>L8</u>	L7 and (fingernails)	1	<u>L8</u>
<u>L7</u>	L6 and (oxyquinoline or petrolatum or lanolin or glycerin)	56	<u>L7</u>
<u>L6</u>	L5 and (ointment)	125	<u>L6</u>
<u>L5</u>	L4 and (benzalkonium adj chloride)	219	<u>L5</u>
<u>L4</u>	L3 and (sodium adj hydroxide)	14362	<u>L4</u>
<u>L3</u>	calcium adj hydroxide	29579	<u>L3</u>
<u>L2</u>	L1	0	<u>L2</u>

DB=EPAB; PLUR=YES; OP=OR

<u>L1</u>	(fingernails) and (calcium adj hydroxide) and (sodium hydroxide)	0	<u>L1</u>
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L9: Entry 2 of 2

File: USPT

Sep 29, 1987

US-PAT-NO: 4696946

DOCUMENT-IDENTIFIER: US 4696946 A

TITLE: Topical Treatment of hyperproliferative skin diseases

DATE-ISSUED: September 29, 1987

INVENTOR-INFORMATION:

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ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
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APPL-NO: 06/ 772077 [PALM]

DATE FILED: August 30, 1985

INT-CL: [04] A61K 31/19, A61K 31/41

US-CL-ISSUED: 514/574; 514/381, 514/561, 514/562, 514/568, 514/572, 514/863

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FIELD-OF-SEARCH: 514/574, 514/381, 514/561, 514/562, 514/568, 514/572, 514/863

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

Search Selected**Search ALL**

	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
<input type="checkbox"/>	<u>2994662</u>	August 1961	Calhoon et al.	252/48.6
<input type="checkbox"/>	<u>3828086</u>	August 1974	Kenney et al.	260/413
<input type="checkbox"/>	<u>4061634</u>	December 1977	Mod et al.	544/158
<input type="checkbox"/>	<u>4153726</u>	May 1979	Borggreffe et al.	514/574
<input type="checkbox"/>	<u>4461775</u>	July 1984	Stanley et al.	424/311
<input type="checkbox"/>	<u>4469705</u>	September 1984	Stanley et al.	424/312

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
2101594	January 1983	GB	260/399

OTHER PUBLICATIONS

J. American Chemical Society, vol. 79, 1957, pp. 362-365, Koenig et al.
Chemical Abstracts, vol. 56, 1962, Subject Index, p. 25N.
Koenig et al., Ind. Eng. Chem., 47, 216, 1955, 362-5.
Tetrahedron Letters, vol. 23, No. 34, pp. 3463-3466, (1982), E. J. Corey et al.

ART-UNIT: 125

PRIMARY-EXAMINER: Schenkman; Leonard

ABSTRACT:

A method for the topical treatment of hyperproliferative skin diseases in a human is described.

Compounds and compositions for use in this method are also described.

13 Claims, 0 Drawing figures

Exemplary Claim Number: 1

BRIEF SUMMARY:

1 BACKGROUND OF THE INVENTION

2 Psoriasis is a hyperproliferative disease of the skin, whose etiology is unknown. The skin lesions associated with psoriasis may be described as dull red patches or plaques of scaly erythema. The scales are distinctive, having a slightly opalescent silvery appearance. The disease has a predilection for certain areas of the body; thus the scalp, the extensor surfaces of the extremities (particularly at the elbows and knees), the back and the buttocks are most usually affected. However, the nails, eyebrows, axillae, umbilicus and anogenital regions are also frequent sites of involvement.

3 To date, there has been no report of a complete and permanent cure for psoriasis, and although the several treatments of choice available afford temporary remission of the symptoms, recurrence is almost certain. Most treatments involve the topical application of steroid (e.g. the adrenocortical steroids) ointments and creams, and no clinically successful, long-term, systemic treatment for the disease is currently available.

4 SUMMARY OF THE INVENTION

5 The invention sought to be patented is a process for treating a human being suffering from hyperproliferative skin diseases which comprises the topical administration of an effective amount of a compound having the structural formula I, II or III wherein: ##STR1## T is straight or branched chain alkyl having from 7-15 carbon atoms which may optionally contain from 1-3 non-cumulative double or triple bonds;

6 U is --CH.sub.2 CH.sub.2 --, --CH=CH-- or --C.tbd.C--;

7 V is straight or branched chain alkylene having from 1 to 4 carbon atoms or is a direct bond;

8 W and W.sup.1 may be the same or different and are O or S(O).sub.m. {wherein m is 0, 1 or 2}

9 X and X.sup.1 may be the same or different and are straight or branched chain alkylene having from 2 to 12 carbon atoms which may optionally contain from 1 to 3 non-cumulative double or triple bonds and which may be optionally substituted with the group--NHR.sup.a wherein R.sup.a is hydrogen, alkyl having from 1 to 6 carbon

atoms, COCF.sub.3, CO(CH.sub.2).sub.2 CH(NH.sub.2)CO.sub.2 H, or SO.sub.2 R.sup.b (wherein R.sup.b is alkyl having from 1 to 6 carbon atoms or CF.sub.3)}; R.sup.1 is hydrogen or straight or branched chain alkyl having from 1-6 carbon atoms; R.sup.2 and R.sup.3 may be the same or different and are CH.sub.2 OR.sup.c {wherein R.sup.c is hydrogen, carboxylic acyl having from 1 to 6 carbon atoms, tetrahydropyran-2-yl or COCH.sub.2 CH.sub.2 CO.sub.2 H}, CHO, 2-tetrazolyl, COR.sup.d wherein R.sup.d is hydroxy, alkoxy having from 1 to 6 carbon atoms, OCH.sub.2 OC(O)C(CH.sub.3).sub.3, NHR.sup.e {wherein R.sup.e is hydrogen, alkyl having from 1 to 6 carbon atoms or CH.sub.2 CO.sub.2 H} or SO.sub.3 H with the proviso that at least one of R.sup.2 and R.sup.3 is 2-tetrazolyl or carboxyl; ##STR2## T, U, V, W, X, R.sup.2 and R.sup.3 are defined above; Y is straight or branched chain alkylene having from 1 to 12 carbon atoms which may optionally be substituted with the group OR.sup.c {wherein R.sup.c is defined above} and may optionally contain from 1 to 3 non-cumulative double or triple bonds; ##STR3##

- 10 T, U, V, R.sup.2 and R.sup.3 are defined above; Z and Z.sup.1 may be the same or different and are straight or branched chain alkylene having from 1 to 12 carbon atoms which may optionally contain from 1 to 3 non-cumulative double or triple bonds;
- 11 R.sup.4 is hydrogen, hydroxyl, or is combined with Z to form a double bond as indicated by the dashed line "a" or a cyclopropyl ring as indicated by the dashed lines "b".
- 12 Preferred values for the above-defined substituents are as follows:
- 13 T is straight chain alkyl having 7-15 carbon atoms;
- 14 U is --C.tbd.C--;
- 15 V is a direct bond;
- 16 W is O or S;
- 17 W.sup.1 is O or S;
- 18 X is alkyl having from 2 to 8, more preferably 2 to 6 carbon atoms;
- 19 X.sup.1 is alkyl having from 2 to 8, more preferably 2 to 6 carbon atoms;
- 20 R.sup.1 is hydrogen;
- 21 R.sup.2 is carboxyl;
- 22 R.sup.3 is carboxyl;
- 23 Y is alkyl having from 2 to 6 carbon atoms;
- 24 Z is alkyl having from 2 to 6 carbon atoms;
- 25 Z.sup.1 is alkyl having from 2 to 6 carbon atoms;
- 26 R.sup.4 is hydrogen, hydroxyl or is combined with Z to form a double bond.
- 27 A preferred subgenus of compounds for use in the process of the invention is represented by a compound having structural formula I, II or III wherein the substituents T-U-V- are combined to form the n-1-tetradecyn-1-yl group, i.e. n-C.sub.12 H.sub.25 C.tbd.C-.
- 28 An additional preferred subgenus of compounds a compound having structural formula I, II or III wherein the substituents R.sup.2 and R.sup.3 may be the same or different and are COR.sup.d wherein R.sup.d is defined above.
- 29 Preferred species of compounds for use in the process of the invention are those having the following names:

- 30 1-propane, 3,3'-{(2-pentadecynylidene)bis(oxy)}biscarboxylic acid;
- 31 1-methane, 1,1'-{(2-pentadecynylidene)bis(oxy)}biscarboxylic acid;
- 32 1-pentane, 5,5'-{(2-pentadecynylidene)bis(oxy)}biscarboxylic acid;
- 33 (.-.-)-1-butane, 3,3'-{(2-pentadecynylidene)bis(oxy)}biscarboxylic acid;
- 34 1-butane, 4,4'-{(2-pentadecynylidene)bis(oxy)}biscarboxylic acid;
- 35 (.-.-)-1-hexane, 5,5'-{(2-pentadecynylidene)bis(oxy)}biscarboxylic acid;
- 36 (.-.-)-6-(4-oxybutan-1-ol)-5-oxaeicos-7-yn-1-oic acid;
- 37 1-propane, 3,3'-{(2-pentadecynylidene)bis(thio)}-biscarboxylic acid;
- 38 1-butane, 4,4'-{(2-pentadecynylidene)bis(thio)}-biscarboxylic acid;
- 39 (.-.-)-1-pentane, 4,4'-{(2-pentadecynylidene)bis(oxy)}biscarboxylic acid;
- 40 (.-.-)-6-(carboxyethylthio)-7-yne eicosanoic acid;
- 41 (.-.-)-6-(carboxypropylthio)-7-yne eicosanoic acid;
- 42 (+) and (-)-6-(carboxypentylthio)-7-yne eicosanoic acid;
- 43 (.-.-)-6-(carboxypentylthio)-7-yne eicosanoic acid;
- 44 6-hydroxy-6-(tetradec-1-ynylidene)-1,11-undecanedicarboxylic acid;
- 45 6-(tetradec-1-ynylidene)-1,11-undecanedicarboxylic acid;
- 46 6-(tetradec-1-ynylidene)-1,11-undec-5(E) and (Z)ene dicarboxylic acids;
- 47 (.-.-)-1-butane, 3,3'-{(2-pentadecynylidene)bis(thio)}biscarboxylic acid; and
- 48 (.-.-)-1-pentane, 4,4'-{(2-pentadecynylidene)bis(thio)}biscarboxylic acid.
- 49 Examples of hyperproliferative skin diseases are psoriasis, lichenified eczema and seborrhoeic dermatitis.

50 DESCRIPTION OF THE INVENTION

- 51 The compounds useful in the process of the invention having structural formula I may be prepared by reacting a compound having structural formula X with a compound having the structural formula XI, ##STR4## wherein T, U, V, W, X, R.sup.1 and R.sup.2 are as defined herein and R' is any convenient alkyl group, preferably ethyl. The carbonyl compound which corresponds to compound X, i.e., T-U-V-COR.sup.1, may optionally be utilized in this reaction in place of compound X. This reaction is preferably carried out under conditions whereby the reaction-produced alcohol, R'OH, or water is continuously removed as it is formed. This continuous removal may be accomplished by azeotropic distillation using a solvent such as benzene or toluene. The reaction proceeds best when catalyzed by acid, e.g. p-toluenesulfonic acid may be utilized; When an excess (i.e. 2 equivalents or more) of reactant XI is utilized, compounds having structural formula I wherein --W--X--R.sup.2 and --W.sup.1 --X.sup.1 --R.sup.3 are equivalent will be produced. When compounds having structural formula I wherein --W--X--R.sup.2 and --W.sup.1 --X.sup.1 --R.sup.3 are different are desired, the reaction may be accomplished in two separate steps utilizing one equivalent of the desired reactant, XI, in each step. In an additional method, a compound having structural formula I where W and W.sup.1 are both oxygen may be treated with one equivalent of a compound having structural formula XI wherein W is sulfur to thereby displace either the W--X--R.sup.2 or the W.sup.1 --X.sup.1 --R.sup.3 substituent. For purposes of this procedure, the W--X--R.sup.2 and W.sup.1

--X.sup.1 --R.sup.3 substituents of starting compound I should ideally be equivalent. This procedure is conveniently carried out using an acid catalyst such as boron trifluoride. Compounds having structural formula I wherein W and W.sup.1 are sulfur may be oxidized to the corresponding sulfoxide or sulfone by known procedures.

- 52 Compounds having structural formula II may be prepared from a compound having formula XII, wherein T, U, V, Y and R.sup.3 are defined above. ##STR5##
- 53 Compounds having structural formula II wherein W is sulfur may be prepared by first converting the hydroxyl substituent of compound XII to a more readily displacable substituent, e.g. the methane sulfonic acid ester, XIII, ##STR6## or to the corresponding bromo or an activated phosphorous substituent.
- 54 The conversion of XII to XIII may be carried out by treating XII with methane sulfonyl chloride under standard conditions. Compound XIII may then be treated with a compound having structural formula XIV. ##STR7## using known conditions to produce the desired compounds having structural formula II wherein W is sulfur. The sulfur atom may thereafter be oxidized to the corresponding sulfoxide or sulfone by known procedures if desired.
- 55 Compounds having structural formula II wherein W is oxygen may be prepared from compound XIII in a similar manner by using the alcohol XV ##STR8## Alternatively, compound XII may be converted to compound II wherein W is oxygen by direct alkylation on the hydroxyl oxygen atom. Thus, for example, XII may be treated with a base such as sodium hydride to form the corresponding sodium salt of the alcohol, XVI. ##STR9## This salt may next be treated with a halide compound, for example, an iodo compound such as IXR.sup.2 to produce the compounds having structural formula II wherein W is oxygen.
- 56 Compounds having structural formula III may be prepared by reacting an anion derived from a compound having structural formula XVII, ##STR10## i.e. compound XVIII ##STR11## wherein M⁺ is a metal cation such as the lithium cation, or an equivalent complex metal cation, e.g. MgBr⁺ with a carbonyl compound having structural formula XIX ##STR12## using known procedures. This reaction will produce compounds having structural formula III wherein R.sup.4 is a hydroxyl group. This tertiary alcohol function may thereafter be converted to other R.sup.4 substituents by known methods if desired. For example, treatment of the tertiary alcohol with diethylaminosulfur trifluoride will produce the corresponding compound wherein R.sup.4 is fluorine. The tertiary alcohol may be dehydrated to produce a compound wherein R.sup.4 and Z are combined to form a double bond, i.e. a compound having structural formula III wherein the dashed line "a" indicates a double bond. This double bond compound may be reduced to produce the compounds wherein R.sup.4 is hydrogen, or it may be reacted with methylene carbene to produce the corresponding cyclopropyl compounds, i.e. a compound having structural formula III wherein the dashed lines "b" indicate the completion of a cyclopropyl ring.
- 57 In certain of the above-described reactions certain substituents may have to be protected in order to avoid unwanted reactions. Thus, for example, certain of the R.sup.2 and R.sup.3 substituents may be protected by art recognized methods. In addition, certain of the groups, R.sup.2 and R.sup.3 may be modified, if desired, by known procedures. Thus, for example, a compound wherein R.sup.2 is CH.sub.2 OH may be converted to a compound wherein R.sup.2 is CO.sub.2 OH by oxidation or to a compound wherein R.sup.2 is CH.sub.2 OCOCH.sub.3 by acylation.
- 58 For purposes of completeness, the following abbreviated reaction sequence is utilized to exemplify a process for performing selective reactions where multiple sites of unsaturation are present. Other such sequences are known in the art. ##STR13##
- 59 In the above abbreviated reaction sequence, THP indicates the 2-tetrahydropyranyl radical. Double bonds can be regiospecifically included or excluded by proper choice of carbon to carbon bond forming reactions and reagents which will be known to those skilled in the art.

- 60 The above-described starting materials are either known compounds or preparable from known compounds by art-recognized methods.
- 61 Thus, compound X is an acetal or ketal, which compounds are preparable from the corresponding aldehyde or ketone by well know methods. In an alternate method, a compound such as XX may be reacted with an orthoester such as ethyl orthoacetate by known methods to produce the acetal XXI. ##STR14##
- 62 Compounds having structural formula XII are secondary alcohols which may be prepared, for example, by the reaction of a Grignard reagent such as XXII with an aldehyde such as XXIII. ##STR15## Known equivalent reactants to XXII such as lithium reagents, e.g. XXIV, may also be utilized. ##STR16##
- 63 Certain compounds of the invention form pharmaceutically acceptable salts with any of a variety of inorganic and organic bases. Suitable bases for purposes of the invention, are those which form pharmaceutically-acceptable salts such as sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, calcium hydroxide, ammonia and amines. The salt forms may be converted back to their respective acid forms by treatment with an acid such as dilute hydrochloric acid. The acid forms and their respective salts differ in certain physical properties such as solubility but they are otherwise equivalent for purposes of the invention.
- 64 Certain compounds useful in the process of the invention form pharmaceutically acceptable salts with organic and inorganic acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic, and the like. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to product a salt in the conventional manner. The free base forms may be regenerated by treating the salt form with a base. For example, dilute aqueous base solutions may be utilized. Dilute aqueous sodium hydroxide, potassium carbonate, ammonia, and sodium bicarbonate solutions are suitable for this purpose. The free base forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but the salts are otherwise equivalent to their respective free base forms for purposes of the invention.
- 65 The compounds useful in the process of the invention may exist in unsolvated as well as solvated forms, including hydrated forms. In general, these solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like are equivalent to the unsolvated forms for purposes of the invention.
- 66 Certain compounds useful in the process of the invention may exist in isomeric forms. The invention contemplates all such isomers both in pure form and in admixture, including racemic mixtures.
- 67 When used herein, the term "treating" means the topical administration to a person suffering from a hyperproliferative skin disease, e.g. psoriasis, of a compound of the formula I, II or III defined herein and the pharmacologically acceptable addition salts thereof. As a result of the topical administration of a compound or salt of the above formula I, II or III a remission of the symptoms of the psoriatic patient, in most cases, can be expected. Thus, one affected by psoriasis can expect a decrease in scaling, erythema, size of the plaques, pruritus and other symptoms associated with psoriasis. The dosage of medicament and the length of time required for successfully treating each individual psoriatic patient may vary, but those skilled in the art of medicine will be able to recognize these variations and adjust the course of therapy accordingly.
- 68 Included within the invention are topical applications on skin whereby the compounds having structural formulas I, II and III are effective in the treatment and control of skin diseases characterized by rapid rates of cell proliferation and/or abnormal cell proliferation, e.g. psoriasis.
- 69 In a preferred method of carrying out the invention a pharmaceutical formulation

comprising a compound having structural formulas I, II or III together with a non-toxic, pharmaceutically acceptable topical carrier, usually in concentrations in the range of from about 0.001 percent to about 10 percent, preferably from about 0.1 percent to about 5 percent, is applied several times daily to the affected skin until the condition has improved. Topical applications may then be continued at less frequent intervals (e.g. once a day) to control mitoses in order to prevent return of severe disease conditions.

- 70 The compounds of formulas I, II and III are conveniently applied in a liquid solvent, preferably in a water-miscible liquid carrier made up of hydrophylic liquids having a high solvating action, e.g. a solution which comprises for example, propylene glycol and polyethylene glycol. The compounds of formulas I, II or III may also be applied in dry form i.e. as a powder. In general, the compounds may be applied in any topical form including creams, lotions, aerosols, dusts, powders and ointments, which are prepared by combining an active ingredient defined by formula I, II or III with conventional pharmaceutical diluents and carriers commonly used in topical dry, liquid, cream and aerosol formulations.
- 71 The pharmaceutical formulations are made according to known procedures, some of which are described in detail in the Examples hereinbelow. Typical formulations include ointments, lotions, creams, sprays, powders, and aerosols. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Such bases may, thus, for example, include water and/or an oil such as liquid paraffin or a vegetable oil such as peanut oil or castor oil. Thickening agents which may be used according to the nature of the base include soft paraffin, aluminum stearate, cetostearyl alcohol, propylene glycol, polyethylene glycols, woolfat, hydrogenated lanolin, beeswax, etc.
- 72 Lotions may be formulated with an aqueous or oily base and will, in general, also include one or more of the following, namely, stabilizing agents, emulsifying agents, dispersing agents, suspending agents, thickening agents, coloring agents, perfumes and the like.
- 73 Powders may be formed with the aid of any suitable powder base, e.g. talc, lactose, starch, etc. Drops may be formulated with an aqueous base or nonaqueous base also comprising one or more dispersing agents, suspending agents, solubilizing agents, etc.
- 74 The topical pharmaceutical compositions according to the invention may also include one or more preservatives or bacteriostatic agents, e.g. methyl hydroxybenzoate, propyl hydroxybenzoate, chlorocresol, benzalkonium chlorides, etc.
- 75 The compositions according to the invention may also contain other active ingredients such as antimicrobial agents, particularly antibiotics, anesthetics, analgesics and antipruritic agents for example.
- 76 The following formulations exemplify some of the dosage forms in which the anti-psoriasis agents of the invention may be employed. In each, the active ingredient is a compound having structural formula I, II or III as is referred to as "active compound".
- 77 FORMULATIONS

Formulation I: Ointment

Formula mg/g

Active Compound	1.0-20.0
Benzyl Alcohol, NF	10.0
Mineral Oil, USP	50.0
White <u>Petrolatum</u> , USP	to make

1.0 g

78 Procedure

- 79 Mix and heat to 65.degree. C., a weighted quantity of white petrolatum, mineral oil, benzyl alcohol, and cool to 50.degree.-55.degree. C. with stirring. Disperse active compound in a portion of the mineral oil and then add to the above mixture with stirring. Cool to room temperature.

Formulation II: Cream	
Formula	mg/g
<hr/>	
Active Compound	1.0-20.0
Stearic Acid, USP	60.0
Glyceryl Monostearate	100.0
Propylene Glycol, USP	50.0
Polyethylene Sorbitan Monopalmitate	50.0
Sorbitol Solution, USP	30.0
Benzyl Alcohol, NF	10.0
Purified Water, USP to make	1.0 g

80 Procedure

- 81 Heat the stearic acid, glyceryl monostearate and polyethylene sorbitan monopalmitate to 70.degree. C. In a separate vessel, dissolve sorbitol solution, benzyl alcohol, water, and half quantity of propylene glycol and heat to 70.degree. C. Add the aqueous phase to oil phase with high speed lightning stirring. Dissolve the active compound in remaining quantity of propylene glycol and add to the above emulsion when the temperature of emulsion is 37.degree.-40.degree. C. Mix uniformly with stirring and cool to room temperature.

Formulation III: Gel	
Formula	mg./g
<hr/>	
Active Compound	1.0-20.0
Propylene Glycol, USP	300.0
Butylated Hydroxytoluene	5.0
Carbomer 940	5.0
Sodium Hydroxide (added as a 1% w/w solution in propylene glycol)	0.7
Polyethylene Glycol 400, USP	669.3-688.

82 Procedure

- 83 Prepare a 1% solution of the sodium hydroxide in propylene glycol and hold. Add approximately one-half the remaining propylene glycol, and the polyethylene glycol 400 to a suitable vessel and mix. Dissolve the butylated hydroxytoluene in this mixture. Disperse the carbomer 940 in the above mixture with vigorous agitation.

Add the solution of sodium hydroxide with high speed agitation to bring pH up to 7 and recirculation until a thick gel forms. Dissolve the active compound in the remaining propylene glycol and add to the gel slowly as the gel is continuously recirculated.

Formulation IV: Lotion		
Formula	mg/g	
Active Compound	1.0-20.0	
Carbomer 940	3.0	
<u>Sodium hydroxide</u> (charged as 4% w/w aqueous solution)	0.05	
Isopropyl Alcohol	40.00	
Purified Water, USP to make	1.0	g

84 Procedure

- 85 Prepare a 4% solution of sodium hydroxide in water. Heat the purified water to 60.degree. C. Add carbomer 940 and mix at high speed until dispersed. Cool the above mixture to room temperature and slowly charge sodium hydroxide until uniform. Add 80% of isopropyl alcohol to the above with mixing. Dissolve the active compound in remaining isopropanol. Add this to the mixture with stirring. Adjust pH to 5.0 to 5.5 with sodium hydroxide, if necessary.

Formulation V: Topical Aerosol		
Formula	mg/g	
Active Compound	1.0-20.0	
Caprylic/Capric Triglyceride	50.00	
Mineral Oil	20.00	
Specially Denatured Alcohol	150.00	
Hydrocarbon Aerosol Propellant	1.0	g
q.s. ad.		

86 Procedure

- 87 Add and mix the caprylic/capric triglyceride mineral oil and specially denatured alcohol in a suitable compounding tank. Add the active compound drug and continue mixing until the active compound is dissolved or dispersed uniformly. Fill the concentrate into cans and then fill the required amount of hydrocarbon aerosol propellant.
- 88 The quantity of active compound in a unit dose of preparation may be varied or adjusted from 1 mg to 100 mg according to the particular application and the potency of the active ingredient. The compositions can, if desired, also contain other therapeutic agents.
- 89 The amount of active compound applied to the involved lesions may be varied depending upon the requirements of the patient, the severity of the condition being treated and the particular compound being employed. Determination of the

proper dosage for a particular situation is within the skill of the art. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

DETAILED DESCRIPTION:

1 EXAMPLE 1

2 2-PENTADECYNYL ALDEHYDE DITHIOACETAL OF CYSTEINE N-TRIFLUOROACETATE METHYL ESTER

3 A solution of the 2-pentadecynyl aldehyde (0.3098 g) in dry CH₂Cl₂ (5 ml) was treated with cysteine methylester N-trifluoroacetate, freshly prepared by zinc reduction of the corresponding disulfide (1 g; required 0.9667 g), followed by trimethylsilyl chloride (0.15 g). The reaction was stirred at room temperature for 1 hour. Evaporation of CH₂Cl₂ in vacuo gave a gummy residue which was distributed between CH₂Cl₂ and water. The CH₂Cl₂ phase was separated, and the aqueous phase extracted once with CH₂Cl₂. Combined CH₂Cl₂ extracts were dried over Na₂SO₄ and evaporated to dryness to provide the crude product which was purified on a coarse silica gel (30 g) column using 20-50% diethyl ether in n-hexane. Yield: 0.6893 g.

4 EXAMPLE 2

5 1-BUTANE-4,4'-{(2-PENTADECYLIDENE) BIS(OXY)} BIS-DIBENZOATE

6 A mixture of 2-pentadecynyl aldehyde diethylacetal (5.0 g), butane-1,4-diol monobenzoate (6.5 g) and p-toluenesulfonic acid (0.2 g) in dry benzene was refluxed with azeotropic removal of ethanol. After 3 hours the dark reaction solution was washed with aqueous NaHCO₃, water, then brine. The solvent was removed in vacuo to give crude product (11.0 g) as a brownish oil which was used as such in the next reaction.

7 EXAMPLE 3

8 1-BUTANOL-4,4'-{(2-PENTADECYLIDENE) BIS(OXY)} BIS

9 The product from Example 2 (4.0 g) was hydrolyzed with 30% KOH in aqueous ethanol (120 ml) by refluxing the reaction mixture for 2 hours. Ethanol was evaporated under vacuum and the residue was washed with water. The product was extracted with diethyl ether, dried over MgSO₄, filtered and evaporated to dryness in vacuo to give 1.8 g of the product as a yellowish oil.

10 EXAMPLE 4

11 1-PROPANE,3,3'-{(2-PENTADECYNYLIDENE) BIS(OXY)}-BISMETHYLCARBOXYLATE

12 A. The acetal-diol (1 g; from Example 3) was dissolved in dry DMF (20 ml) and treated with pyridinium dichromate (8.2 g). The mixture was stirred at room temperature for 20 hours, diluted with 200 ml water and extracted with approximately 400 ml diethylether in portions. Drying over Na₂SO₄ and evaporation of the ether extract gave the crude diacid.

13 The reaction was repeated with acetal-diol (0.488 g) in 10 ml DMF and 4.1 g pyridinium dichromate. Work-up as above gave the crude diacid.

14 B. The two reactions from above were combined and treated with diazomethane (from 6.5 g diazald). Excess diazomethane was removed by carefully bubbling nitrogen through the solution. Evaporation of diethylether gave the crude diester which was chromatographed on TLC grade silica gel (50 g) using 5% acetone in n-Hexane as eluent. The pure dimethylester (0.6813 g) was obtained as a yellowish oil.

15 EXAMPLE 5

16 1-PROPANE, 3,3'-{(2-PENTADECYNYLIDENE) BIS(OXY)}BISCARBOXYLIC ACID

17 The dimethylester (0.5 g; from Example 4) was dissolved in ethanol (10 ml) and treated with 10% aqueous NaOH (5 ml). After stirring at room temperature for 36 hours, ethanol was evaporated in vacuo, the residue taken up in water and extracted once with diethylether. The remaining aqueous phase was acidified to pH 1.5 with aqueous oxalic acid and extracted with CH₂Cl₂. Drying CH₂Cl₂ extract over Na₂SO₄ followed by evaporation in vacuo provided the pure diacid as a colorless crystalline solid, m.p. 62.degree.-63.degree. C. Yield: 0.4496 g.

18 EXAMPLE 6

19 1-BUTANE-4,4'-{(2-NONYLIDENE) BIS(OXY)}BIS-DIBENZOATE

20 A mixture of 2-nonyl aldehyde diethylacetal (4.4 g), butane-1,4-diol monobenzoate (8.2 g) and a catalytic amount of p-toluenesulfonic acid in dry benzene was refluxed for 3 hours as in Example 2. Work-up as in Example 2 gave the crude product which was purified by passing through a SiO₂ column eluting with hexane and chloroform (1:1) to give 9.0 g of the product.

21 EXAMPLE 7

22 1-BUTANOL-4,4'-{(2-NONYLIDENE) BIS(OXY)}BIS

23 The product from Example 6 (1.0 g) was hydrolyzed with 30% KOH in aqueous ethanol as in Example 3. The product so obtained was purified by preparative TLC using 5% methanol in CHCl₃ as eluent. Yield: 0.3 g.

24 EXAMPLE 8

25 1-PROPANE, 3,3'-{(2-NONYLIDENE) BIS(OXY)}BIS-CARBOXYLIC ACID

26 A. The product from Example 7 (0.5 g) was oxidized with pyridinium dichromate (4.1 g) in 13 ml of dry DMF at room temperature for 2 days. The mixture was diluted with water (350 ml), and extracted with diethylether (3.times.100 ml), washed with water, dried (Na₂SO₄) and filtered. The solvent was evaporated to give 0.4 g crude diacid which was methylated with diazomethane followed by chromatography to give pure dimethylester which was hydrolyzed as in Example 5 to give 0.3 g pure diacid.

27 EXAMPLE 9

28 BENZENE METHANOL-4,4'-{2-PENTADECYN-1-YLIDENE BIS(OXY) METHYLENE}BIS

29 The crude reaction mixture containing benzene methanol-4,4'-dibenzoate ester was treated with 100 ml of water, 20 g of KOH and 300 ml of absolute ethanol. After stirring the mixture at room temperature overnight, it was refluxed for one hour. The solvents were then evaporated, the oily residue was treated with CH₂Cl₂, washed with water, and dried over Na₂SO₄. After evaporation of the solvent, the mixture was purified via silica gel chromatography (50% EtOAc/Hexanes). Yield: 8.5 g).

30 EXAMPLE 10

31 BENZOIC ACID-4,4'-{2-PENTADECYN-1-YLIDENE BIS(OXY) METHYLENE}BIS

32 1.7 g of benzoic acid-4,4'-{2-pentadecyn-1-ylidene bis(oxy)methylene}bis-dimethyl ester were stirred at room temperature in 30 ml of absolute EtOH and 20 ml of 10% aqueous KOH. After two days, the solvents were evaporated under reduced pressure. The residue was taken in water and acidified with aqueous oxalic acid. The precipitate obtained was filtered, washed with water and dried. Yield: 1.6 g.

33 EXAMPLE 11

34 A. METHYL-{4-(OXY)-METHYLACETATE}-3-OXAOCETADEC-5-YN-1-OATE

35 B. METHYL-{4-(2-OXYETHANOL)}-3-OXAOCETADEC-5-YN-1-OATE

36 2.0 g of 4-(2-oxyethanol)-3-oxaocetadecen-5yn-1-ol (example 31) in 30 ml dry DMF was added in portion to a solution of pyridinium dichromate (PDC) in 70 ml of dry DMF. After stirring at room temperature for two days, the mixture was poured into water (500 ml). The aqueous solution was extracted several times with Et.sub.2 O. The combined extracts were washed with water and dried over Na.sub.2 SO.sub.4. The crude acid resulting from the evaporation of the solvent was treated in Et.sub.2 O at 0.degree. C. with large excess of diazomethane solution in Et.sub.2 O. The esterified mixture (2.0 g) was purified by chromatography on TLC grade silica gel:

37 Fractions 23-28 gave compound (A), 0.13 g

38 Fractions 75-85 gave compound (B), 0.11 g.

39 EXAMPLE 12

40 PENTANOIC ACID-5,5'-{2-PENTADECYN-1-YLIDENE-BIS(OXY)}BISDIMETHYLESTER

41 A dry DMF solution (50 ml) of 1-pentanol-5,5'-{2-pentadecyn-1-ylidene-bis(oxy)}bis (example 14) (3.67 g) was added at room temperature to a solution of pyridinium dichromate in 120 ml of dry DMF. After two days the reaction was worked up as in Example 11. The crude reaction mixture was treated at 0.degree. C. in Et.sub.2 O with large excess of CH.sub.2 N.sub.2. The excess diazomethane was destroyed with glacial acetic acid and the reaction mixture was purified by silica gel chromatography (10% EtOAc/Hexanes). Yield: 0.9 g.

42 EXAMPLE 13

43 PENTANOIC ACID-5,5'-{2-PENTADECYN-1-YLIDENE BIS(OXY)}BIS

44 0.7 g of pentanoic acid-5,5'-{2-pentadecyn-2-ylidene bis(oxy)}bis-dimethyl ester (example 12) was stirred at room temperature for 24 hours with 10 ml of absolute EtOH and 10 ml of 10% aqueous KOH. The solvents were then evaporated under reduced pressure. The residue was taken in water, acidified with aqueous oxalic acid, and extracted several times with CH.sub.2 Cl.sub.2. The combined extracts were washed with water and dried over Na.sub.2 SO.sub.4. Evaporation of the solvent yielded 0.65 g. of the title compound.

45 EXAMPLE 14

46 1-PENTANOL-5,5'-{2-PENTADECYN-1-YLIDENE-BIS(OXY)}BIS

47 The crude reaction mixture containing 1pentanol-5,5'-{2-pentadecyn-1-ylidene bis(oxy)}bis-dibenzoate ester was stirred overnight with 150 ml of water and 300 ml of absolute EtOH containing 25 g of KOH. After refluxing for three hours, the solvents were evaporated under reduced pressure. The residue was treated with CH.sub.2 Cl.sub.2, washed with water and dried over Na.sub.2 SO.sub.4. The reaction mixture was purified by silica gel chromatography (50% EtOAc/Hexanes). Yield: 4.0 g.

48 EXAMPLE 15

49 HEXANOIC ACID-6,6'-{2-PENTADECYN-1-YLIDENE BIS(OXY)}BIS

50 3.5 g of 1-hexanol-6,6'-{2-pentadecyn-1-ylidene bis(oxy)}bis in 20 ml of dry DMF was added in portions to a solution of pyridinium dichromate in 70 ml of dry DMF at room temperature. After 24 hours, the reaction was worked up as Example 11. The reaction mixture was purified by silica gel chromatography (first CHCl.sub.3 ; then 5% MeOH/CHCl.sub.3). Yield: 70 mg.

51 EXAMPLE 16

52 1-HEXANOL-6,6'-55 2-PENTADECYN-1-YLIDENE BIS(OXY)}BIS

53 The title compound was prepared and purified in similar manner as in Example 14. The starting material was a mixture containing 1-hexanol-6,6'-{2-pentadecyn-1-ylidene bis(oxy)}bis dibenzoate ester.

54 EXAMPLE 17

55 (.+-.)-1-BENZOYLOXY-6-(4-OXYBUTANE-1-OL)-5-OXAECOS-7-YNE

56 3.5 g of benzooyl chloride in 27 ml of CH₂Cl₂ was added dropwise, over a period of three hours, at 0.degree. C. to a solution of 1-butanol-4,4'-{2-pentadecyn-1-ylidene bis(oxy)}bis (8.0 g) and dry pyridine (15 ml) in 60 ml of CH₂Cl₂. After the addition, the mixture was allowed to warm to room temperature and stirred overnight. The mixture was then diluted with CH₂Cl₂ (400 ml), washed with water, and dried over Na₂SO₄. After evaporation of the solvent, the reaction mixture (10 g) was purified by silica gel chromatography (10% Acetone/CHCl₃). This material was chromatographed again using CHCl₃ as eluent. Yield 4.2 g.

57 EXAMPLE 18

58 (.+-.)-6-(4-OXYBUTAN-1-OL)-5-OXAECOS-7-YN-1-OIC ACID

59 2.2 g of product from Example 17 was oxidized and purified as in Example 15 (eluent: first CHCl₃, then 1% MeOH/CHCl₃). The product of the oxidation (1.1 g) was hydrolysed and the reaction was worked up as in Example 14. The reaction product was purified by column chromatography (SiO₂; eluent: first CHCl₃; then 50% CH₃CN/CHCl₃; then 30% MeOH/CHCl₃). The product obtained from the elution with 30% MeOH/CHCl₃ was purified again (SiO₂ 5% MeOH/CHCl₃) using the same technique. Yield: 0.16 g.

60 EXAMPLE 19

61 6-(4-OXY-METHYLBUTANOATE)-5-OXA-METHYL EICOSANOATE

62 1.7 g of butanoic acid-4,4'-{2-pentadecyn-1-ylidene bis(oxy)}bis-dimethylester was dissolved in olefin free petroleum ether (60 ml) and hydrogenated in the presence of 10% Pd/C (0.7 g). After absorption of H₂ was complete (3 hours), the catalyst was filtered through celite and washed with CH₂Cl₂. The reaction product (1.6 g) obtained after evaporation of the combined filtrates was purified by silica gel chromatography (1% acetone in CHCl₃). Yield: 0.8 g.

63 EXAMPLE 20

64 6-(4-OXYBUTANOIC ACID)-5-OXAECOSANOIC ACID

65 0.65 g of the product from example 19 was hydrolyzed in 12 ml of absolute EtOH and 8.1 ml of 10% aqueous KOH as in example 13 to provide the pure diacid.

66 EXAMPLE 21

67 (.+-.)-1-BENZOYLOXY-6-ETHOXY-5-OXAECOS-7-YNE

68 32 g of ethane-2,2'-{2-pentadecyn-1-ylidene bis(oxy)}bis, 25 g of 4-benzoyloxy-1-butanol, and 100 mg of p-toluene sulfonic acid were refluxed in a dry apparatus in 300 ml of benzene using a Dean-Stark trap. After evaporating 75 ml of solvent, the solution was cooled to room temperature diluted with CHCl₃, washed with saturated aqueous NaHCO₃, then with water and dried over Na₂SO₄. The resulting oil (13 g) after evaporation of the solvent was purified by column chromatography (SiO₂) (CHCl₃). The partially purified compound was rechromatographed (SiO₂) (50% Hexanes/CHCl₃). Yield: 1.5 g.

69 EXAMPLE 22

70 (.-.-)-6-ETHOXY-5-OXAEICOS-7-YN-1-OL

71 (.-.-)-1-Benzoyloxy-6-Ethoxy-5-oxaeicos-7-yne was hydrolyzed using the same procedure as described for example 14. The reaction mixture was purified in the same manner using CHCl₃ as eluent.

72 EXAMPLE 23

73 (.-.-)-6-ETHOXY-5-OXAEICOS-7-YN-1-OIC ACID

74 1.2 g of the product from example 20 in 15 ml of dry DMF was added in portions to a solution of pyridinium dichromate (4.4 g) in 30 ml of dry DMF. The solution was stirred at room temperature for 24 hours, then poured into water (300 ml). The aqueous mixture was extracted several times with Et₂O, the combined extracts were washed with water and dried over Na₂SO₄. The reaction mixture was purified by column chromatography (SiO₂) (1% MeOH/CHCl₃). The partially purified product (0.54 g) was further purified by preparative thin layer chromatography (SiO₂) (2% MeOH/CHCl₃). Yield: 0.35 g.

75 EXAMPLE 24

76 4-METHYL-6-(4-OXYPENTANOL)-5-OXAEICOS-7-YN-1-OL

77 The crude mixture containing 1-Pentanol-4,4^{sup.1}-{2-Pentadecyn-1-ylidene-Bis(oxy)}bis-dibenzoate ester was hydrolyzed and purified using the same procedure as described for example 14 to provide the title compound.

78 EXAMPLE 25

79 PENTANOIC ACID-4,4'-{2-PENTADECYN-1-YLIDENE BIS(OXY)}-BIS

80 2.6 g of Pentanoic acid-4,4'-{2-Pentadecyn-1-ylidene bis(oxy)}bis-dimethyl ester was hydrolyzed using the same procedure as described in example 13. Yield: 2.3 g.

81 EXAMPLE 26

82 5-METHYL-7-(5-OXYHEXANOL)-6-OXAHENEICOS-8-YN-1-OL

83 The mixture containing 5-Methyl-7-(5-oxyhexanol)-6-oxaheneicos-8-yn-1-ol-dibenzoate ester was hydrolyzed and purified using the same procedure as described in example 14.

84 EXAMPLE 27

85 METHYL-{5-METHYL-7-(5-OXY-METHYLHEXANOATE)}-6-OXAHENEICOS-8-YN-1-OATE

86 The product from example 24 was oxidized, methylated and purified as described in example 12.

87 EXAMPLE 28

88 5-METHYL-7-(5-OXYHEXANOIC ACID)-6-OXAHENEICOS-8-YN-OIC ACID

89 The product from example 27 was hydrolyzed using the same procedure as described for example 13.

90 EXAMPLE 29

91 CIS-METHYL-6-(4-OXY-METHYLBUTANOATE)-5-OXAEICOS-7-EN-1OATE

92 0.4 g of Lindlar catalyst in petroleum ether (10 ml; olefin and sulfur free) was equilibrated under H₂ at room temperature and atmospheric pressure (containing 5 drops of a 5% solution of quinoline in petroleum ether). After four

hours, 1.0 g of butanoic acid-4,4'-{ 2-pentadecyn-1-ylidene bis(oxy)}bis-dimethyl ester in 20 ml of petroleum ether (olefin and sulfur free) was added. The mixture absorbed 47 ml of H.sub.2 (theory: 55 ml). The catalyst was then removed by filtration through "Celite" and washed several times with petroleum ether. Evaporation of the solvent yielded 0.9 g of the title compound.

93 EXAMPLE 30

94 POTASSIUM-6-(4-OXY-POTASSIUM BUTANOATE-5-OXAECOS-7-EN-1-OATE

95 0.6 g of product from example 29 was dissolved in 15 ml of absolute EtOH and 8 ml of 10% aqueous KOH was added. After stirring at room temperature for 24 hours, the solvents were evaporated and the residue was applied as water solution to 65 g of XAD-4 resin column. The column was eluted first with water, then with MeOH. The fractions containing the compound were combined and treated twice with 30% Et.sub.2 O/Hexanes. The solvents were decanted and the remaining product dried in vacuo to provide the title compound.

96 EXAMPLE 31

97 4-(2-OXYETHANOL)-3-OXAOCETAD-5YN-1-OL

98 The reaction mixture containing ethanol-2,2'-{pentadecyn-1-ylidene bis(oxy)}bis-dibenzoate ester was hydrolyzed and purified using the same procedure as described in example 14.

99 EXAMPLE 32

100 4-(OXYACETIC ACID)-3-OXAOCETAD-5-YN-1-OIC ACID

101 0.13 g of methyl-{4-(oxy-methylacetate)}-3-oxaoctadec-5-yn-1-oate (example 11) was hydrolyzed using the same procedure described in example 13. Yield: 0.13 g.

102 EXAMPLE 33

103 L-CYSTEINE, S{R or S}-{1-METHOXY-4-OXOBUTOXY}-2-NONYNYL}-N-(TRIFLOUROACETYL) METHYLESTER-(LESS POLAR ISOMER) and L-CYSTEINE, S{R or S}-{1-(4-METHOXY-4-OXOBUTOXY)-2-NONYNYL}-N-(TRIFLOUROACETYL) METHYLESTER-(MORE POLAR ISOMER)

104 A solution of the acetal-dimethylester (0.6627 g from example 8-A) in dry CH.sub.2 Cl.sub.2 (5 ml) was treated with freshly prepared cysteine methylester N-trifluoroacetamide (from 0.4300 g corresponding disulfide) and the mixture cooled (dry ice/cyclohexanone bath). With stirring and in an atmosphere of N.sub.2, BF.sub.3. Et.sub.2 O (0.05 ml) was syringed in. After 1 hour the reaction flask was allowed to stir outside the cooling bath for about 3 minutes and then quenched with dilute (about 7%) NH.sub.4 OH solution. Extractive isolation with CH.sub.2 Cl.sub.2 gave a gummy product (0.9797 g) which was chromatographed on TLC grade silica gel (50 g) using 10% acetone /n-Hexane as eluent. Fractions (5 ml each):

105 41-51 Pure less polar isomer (0.1287 g)

106 61-81 Pure more polar isomer (0.0831 g)

107 Both isomers were obtained as thick oils.

108 EXAMPLE 34

109 L-CYSTEINE, S{R or S}-{1-(4-METHOXY-4-OXOBUTOXY)-2-PENTADECYNYL}-N-(TRIFLOUROACETYL) METHYLESTER-(LESS POLAR ISOMER) AND

110 L-CYSTEINE, S{R or

S}-{1-(4-METHOXY-4-OXOBUTOXY)-2-PENTAECYNYL}-N-(TRIFLOUROACETYL) METHYLESTE R-(MORE POLAR ISOMER)

111 A stirred solution of the acetal-diester (1 g; from example 4) dissolved in dry CH₂Cl₂ (6 ml) was treated with cysteine methylester N-trifluoroacetamide (freshly prepared from 0.53 g corresponding disulfide). The mixture was cooled (cyclohexanone/dry ice bath) and the reaction flask was taken out of the cooling bath and let stir for 3-4 minutes followed by treatment with dilute (about 7%) NH₄OH. Extractive isolation with CH₂Cl₂ gave a gummy product (1.4618 g) which was chromatographed on TLC grade silica gel (75 g) using 10% acetone/n-Hexane as eluent. Fractions (5 ml each):

112 50-58 Pure less polar isomer (0.3783 g)

113 64-78 Pure more polar isomer (0.2626 g)

114 Both isomers were obtained as thick oils.

115 EXAMPLE 35

116 L-CYSTEINE, S{R or S}-{1-(4-POTASSIUM CARBOXYLATE)BUTOXY-2-PENTADECYNYL}POTASSIUM SALT (FROM LESS POLAR DIASTEREOMER)

117 The dimethylester (0.3783 g; from example 32, less polar isomer) was subjected to hydrolysis with 0.13 M K₂CO₃ (100 ml) in MeOH:water (3:1) at room temperature. After about 36 hours solvents were removed in vacuo and the crude dipotassium salt so obtained purified on XAD-4 (140 g) column:

118 Fraction 1, 600 ml-water (discarded)

119 Fractions 2-5, 400 ml each-methanol

120 Evaporation in vacuo provided the product as a amorphous solid, 0.1043 g.

121 EXAMPLE 36

122 L-CYSTEINE S{R or S}-{1-(4-POTASSIUM CARBOXYLATE)-BUTOXY-2-PENTADECYNYL}-POTASSIUM SALT (FROM MORE POLAR DIASTEREOMER)

123 The dimethylester (0.3426 g; from example 34, more polar isomer) was subjected to hydrolysis with 0.13 M K₂CO₃ (100 ml) in MeOH:water (3:1) as in example 35. Work-up and purification on XAD-4 column (140 g) provided in fractions 2-5 (400 ml each, MeOH) the product (0.1049 g) as a amorphous solid.

124 EXAMPLE 37

125 PROPANOIC ACID-4,4'-{4E,6Z,9Z-PENTADECATRIEN-2-YNYLIDENE}BIS(THIO) BIS

126 A solution of the product from preparative example IV (1.0 g) and .gamma.-mercaptobutyric acid (1.1 g) in 24 ml of dry CH₂Cl₂ was cooled to -22.degree. C. (CCl₄/CO₂) (under N₂). To this was added BF₃Et₂O (0.5 ml). The reaction mixture was stirred at this temperature for 2 hours. The mixture was diluted with CH₂Cl₂ and washed with water. The organic phase was dried (Na₂SO₄) and concentrated to provide the crude product which was purified by passing through 65 g of coarse SiO₂ column, using CHCl₃:MeOH:AcOH (990:9:1) as eluent to yield 0.98 g of product.

127 EXAMPLE 38

128 1-PENTANE-5,5'-{(2-PENTADECYLIDENE) BIS(THIO)}-BISCARBOXYLIC ACID

129 The product from preparative example II (2.0 g) in CH₂Cl₂ (15 ml) was treated with 1-mercapto-5-carbomethoxy-pentane (3.9 g) under N₂ at room temperature. To this was added Me₃SiCl (1.5 ml) and the reaction was allowed

to stir at room temperature for 1/2 hour. The solvent was removed under vacuum and the residue was purified on a SiO₂ column with gradient elution (hexane; 2% Et₂O/hexane; 5% Et₂O/Hexane; 10% Et₂O/Hexane) to give 3.2 g of product.

130 EXAMPLE 39

131 1-PROPANE-3,3'-{(2-PENTADECYLIDENE) BIS (THIO)}-BISCARBOXYLIC ACID

132 The product from preparative example II (1.58 g) and .gamma.-mercaptobutyric acid (2.3 g) in 10 ml of dry CH₂Cl₂ was treated with Me₃SiCl (1.0 ml) as in Example 38 to afford 1.35 g of product.

133 By reacting the product from preparative example II respectively with an excess of .DELTA.-mercaptopentanoic acid or .gamma.-mercaptopentanoic acid by the method of example 39, 1-butane-4,4'-{(2-pentadecylidene)bis(thio)}-bis-carboxylic acid and (.+-.)-1-pentane-4,4'-{(2-pentadecylidene)bis(thio)}-bis-carboxylic acid were obtained.

134 EXAMPLE 40

135 1-PROPYNL-3,3'-{2-PENTADECYN-1-YLIDENE-BIS(OXY)}BIS

136 5.0 g of 2-pentadecynal diethyl acetal (preparative example I), 13 ml of propargylic alcohol, and 0.2 g of p-toluene sulfonic acid were refluxed in 200 ml of benzene using a Dean-Stark trap provided with an adapter filled with Drierite. After distilling 170 ml of azeotrope, the residue is diluted with hexanes (200 ml). The organic phase was washed first with aqueous NaHCO₃, then with water, dried (Na₂SO₄) and evaporated in vacuo to provide the crude product. It was purified by column chromatography (SiO₂) eluting first with hexanes (1000 ml), then 3% EtOAc/Hexanes. Yield: 2.4 g.

137 EXAMPLE 41

138 1-BUTANOL 4,4'-{(TRIDECYLIDENE) BIS (OXY)}BIS-BENZOATE

139 To a 3 neck, 100 ml reaction vessel were added: catalytic amount of .rho.-toluenesulfonic acid monohydrate (50 mg), 8.54 g of butane 1,4-diol monobenzoate, and 5 g tridecenal, all in a total 25 ml benzene. The reaction mixture was heated to reflux with azeotropic removal of water. After .about.2 hours the reaction was cooled, the benzene solution washed with aqueous K₂CO₃ followed by distilled water. The organic phase was dried over Na₂SO₄ and evaporated to dryness in vacuo. The crude product so obtained was chromatographed on coarse silica gel (500 g) using 5% acetone in n-Hexane as eluent. Fractions 14 and 15 (200 ml each) were evaporated in vacuo to provide pure dibenzoate (4.23 g) as a thick oil.

140 EXAMPLE 42

141 1-BUTANOL, 4,4'-{(TRIDECYLIDENE) BIS (OXY)}

142 A solution of the dibenzoate (1 g; from example 39 in ethanol (20 ml) was treated with aqueous 10% NaOH solution. An additional 20 ml ethanol was added to obtain a homogenous solution. After stirring at room temperature for .about.48 hours, the reaction was worked up as in example 3 to provide virtually pure product as a yellowish oil. It was used as such in the next reaction.

143 EXAMPLE 43

144 1-BUTANOIC ACID, 4,4'-{(TRIDECYLIDENE) BIS (OXY)}BIS-METHYL CARBOXYLATE

145 The diol (1 g; from example 40) was oxidized with pyridinium dichromate (7.33 g) in dry DMF (14 ml) as in example 4A to provide crude diacid which was treated with diazomethane as in example 4B. Chromatography of the crude dimethylester on TLC grade silica gel (30 g) using 5% acetone in n-Hexane as eluent provided the pure

dimethylester (0.28 g) as a yellow oil.

146 EXAMPLE 44

147 1-BUTANOIC ACID, 4,4'-{(TRIDECYLIDENE) BIS(OXY)} BIS

148 A solution of the dimethylester (0.2 g; from (example 41) in ethanol was treated with 10% aqueous NaOH (2 ml) and the mixture refluxed for 4 hours. Work-up of the reaction as in example 5 yielded the pure diacid (0.15 g) as a crystalline solid, m.p. 33.degree. C.

149 EXAMPLE 45

150 6-(CARBOXYPROPYLTHIO)-7-YNE-EICOSANOIC ACID

151 A mixture of methyl-6-bromo-7-yne-eicosanoate (3.0 g), methyl .delta.-mercaptobutyrate (1.0 g), Cs.sub.2 CO.sub.3, (2.44 g) in DMF (70 ml) was stirred at room temperature for 2 hours. After dilution with water followed by extraction with Et.sub.2 O afforded 4.0 g crude product which was purified on SiO.sub.2 (200 g) column. Elution with 50% hexane/CHCl.sub.3 gave 1.7 g pure eicosanoate.

152 The diester (1.42 g) from above was hydrolyzed with 10 ml 10% KOH and 20 ml EtOH at room temperature for 5 hours. After work-up as in example 5, the pure diacid was obtained as a solid (1.22 g).

153 EXAMPLE 46

154 6-(CARBOXPENTYLTHIO)-7-YNE-EICOSANOIC ACID

155 A mixture of methyl-6-bromo-7-yne-eicosanoate, 1-mercapto-5-carbomethoxy-pentane (1.21 g) in 70 ml DMF was treated with Cs.sub.2 CO.sub.3 (2.44 g) as in Example 45 to give 1.02 g of methyl-6-(methylcarboxypentylthio)-7-yne-eicosanoate.

156 The diester (0.72 g) from above was hydrolyzed in a similar manner as in Example 45 to give the title compound as a solid (0.53 g).

157 EXAMPLE 47

158 6-(CARBOXYETHYLTHIO)-7-YNE-EICOSANOIC ACID

159 To a stirred slurry of 0.58 g of NaH (50%) in Et.sub.2 O (12 ml) at 0.degree. C. was added dry CF.sub.3 CH.sub.2 OH (0.93 ml). After the H.sub.2 evolution had ceased, a solution of triphenylphosphine (1.58 g) in 12 ml of CH.sub.2 Cl.sub.2 was added. After stirring for 10 min, 0.3 ml bromine was added. This mixture was then stirred at 0.degree. C. for 1 hour, followed by addition of a solution of the product from preparative example VI (1.7 g) and methyl-3-mercaptopropionate (0.55 ml) in CH.sub.2 Cl.sub.2 (2.5 ml). The mixture was stirred at room temperature for 7 hours. The reaction was quenched with water and extractive isolation with CH.sub.2 Cl.sub.2 yielded 2.5 g crude product. Chromatography on 100 g SiO.sub.2 using 30% hexane in CH.sub.2 Cl.sub.2 as eluent gave 0.66 g of methyl-6-(methylcarboxy-ethylthio)-7-yne-eicosanoate.

160 The above product (1.3 g) was hydrolyzed with 12.2 ml of 10% NaOH in 25 ml EtOH at room temperature for 17 hours. Work-up as in example 5 yielded 0.91 g of the product as a yellowish solid.

161 EXAMPLE 48

162 6-{2-(N-TRIFLUOROACETYLAMINO)-ETHYLTHIO}-7-POTASSIUM EICOSYNATE

163 The product from example 49 (0.5 g) in 40 ml dry MeOH was treated with 0.5 g of 5-ethylthiotrifluoroacetate and was stirred at room temperature for 1 hour. The MeOH was removed in vacuo to give 0.57 g the title compound as a yellowish liquid.

164 EXAMPLE 49

165 6-(2-AMINOETHYLTHIO)-7-POTASSIUM EICOSYNATE

166 Methyl-6-(N-trifluoroacetylthio)-7-yne-eicosanoate was prepared in a manner similar to example 47, except that trifluoroacetamide-ethanethiol was used instead of methyl-3-mercapto-propionate.

167 The above product (1.0 g) was hydrolyzed with 50 ml of 0.13 M K₂CO₃ in MeOH/H₂O(3:1) at room temperature for 48 hours and subjected to purification on a XAD-4 (250 g) column to yield 0.56 g of product.

168 EXAMPLE 50

169 (.-.) TRANS-5-HYDROXY-6-(CYSTEINYL POTASSIUM SALT)-7-POTASSIUM EICOSYNATE

170 Hydrolysis of (.-.)-methyl-6-(N-trifluoroacetylcysteinyl-methylester)-5-ol-7-eicosynate (0.23 g) in a manner similar to example 49 provided 0.16 g of the title compound.

171 EXAMPLE 51

172 (.-.)-6-(CYSTEINYL METHYL ESTER)-7-EICOSYNOIC ACID

173 (The synthesis of the title compound is described in part E of this example.)

174 Part A

175 To a solution of dry cyclohexanone (20 g) in dry Et₃N (125 ml) in dry DMF (125 ml) was added in one portion 61.2 g of t-butyldimethyl chlorosilane. The mixture was refluxed under N₂ for two days. After cooling to room temperature, the mixture was diluted with Et₂O, washed with aqueous NaHCO₃, then with 0.1 N HCl, then again with saturated aqueous NaHCO₃, and finally with water, and dried over Na₂SO₄. The oil, resulting from the distillation of the solvents, was purified by fractional distillation. Yield: 22 g. B.p.=70.degree.-73.degree. C./4 mm, Hg.

176 Part B

177 A solution of 10 g of the product from part A in 150 ml dry CH₂Cl₂ and 15 ml t-butanol was ozonized at -78.degree. C. for 1/2 hour. The excess O₃ was kept in solution for 15 more minutes, then bubbled off with N₂. (CH₃)₂S (10 ml) was added at -78.degree. C., then the solution was allowed to warm to room temperature and kept overnight. After evaporation of the solvent, the resulting oil was purified by fractional distillation. After distilling the fraction boiling at 44.degree.-50.degree. C./4 mm Hg, the residue was used as such.

178 Part C.

179 14.8 ml of a 3.0 molar solution of EtMgBr in Et₂O was added at room temperature with stirring under N₂ to 10.0 gr of 1-tetradecyne in 20 ml of dry Et₂O. After the addition, the solution was stirred for another hour, then added to a precooled solution (dry ice-acetone bath) of the aldehyde prepared as described in part B (10.0 g) in 75 ml of dry Et₂O. After the addition, the thick paste formed was allowed to warm to room temperature and stirred for one hour; then 75 ml of saturated aqueous NH₄Cl was added in portions. The organic layer was separated, and the aqueous layer extracted several times with Et₂O. The combined extracts were washed with water and dried over Na₂SO₄. The oil resulting from the evaporation of the solvent, was purified by fractional distillation.

180 The fractions distilling between 80.degree. and 100.degree. C. at 3 mm Hg were discarded. The residue was used as such for part D.

181 Part D.

182 5.0 g Of the product prepared as described in part C was dissolved in 50 ml of dry CH₂Cl₂ and 10 ml of dry pyridine and the solution cooled (ice bath). A solution of methanesulfonic anhydride (2.85 g) in 20 ml of dry CH₂Cl₂ was added dropwise. After the addition, the mixture was let warm up and stirred at room temperature for three hours, then diluted with CH₂Cl₂. The CH₂Cl₂ solution was washed twice with water, then with aqueous NH₃ (1:10), then again with water and dried over Na₂SO₄. The reaction product (5.4 g) obtained after evaporation of the solvent was used as such for part E.

183 Part E.

184 2.0 g Of the product prepared as described in part D, t-butanol (7 ml), cysteine methyl ester hydrochloride (1.46 g), and 4 ml of dry Et₃N were mixed in the order under N₂ at room temperature. After 24 hours, 20 ml of dry CH₂Cl₂ was added and the mixture stirred for another 24 hours. The solvents were then evaporated, and the reaction mixture was purified by column chromatography (silica gel). The column was eluted first with CHCl₃ (3 liters), then with 20% MeOH/CHCl₃. The combined fractions containing the compound (2.7 g) were chromatographed again on silica gel. The column was eluted successively with CHCl₃ (1 liter), 5% MeOH/CHCl₃, 10% MeOH/CHCl₃, and 20% MeOH/CHCl₃. The fractions containing the compound were combined and purified by preparative thin layer chromatography on silica gel {solvent: 10% (MeOH:NH₃)/CHCl₃ (9:1); two elutions} yield: 0.05 g.

185 EXAMPLE 52

186 (.+-.)-6-(N-TRIFLUOROACETYL CYSTEINYL METHYL ESTER)-7-EICOSYNE

187 Part A

188 The reaction conditions were the same as in part C of example 51 except that hexanal was used as one of the reactants.

189 Part B

190 The reaction conditions were the same as in part D of example 51.

191 Part C

192 1.99 g of the product as obtained from part B, tert-butanol (10 ml), 2.97 g of cysteine methyl ester N-trifluoroacetate and dry Et₃N (2.5 ml) were reacted as described in example 53. The reaction mixture was purified by column chromatography (silica gel) (CHCl₃). The fractions containing the product were combined and purified again as above using 50% CHCl₃/Hexanes as eluent. The pure fractions were combined to provide the title compound.

193 EXAMPLE 53

194 (.+-.)-6-(N-TRIFLUOROACETYLCYSTEINYL METHYL ESTER)-7-EICOSYNOIC ACID

195 1.97 g of crude product prepared as described in part D of example 51, tert-butanol (7 ml), N-trifluoroacetyl cysteine methyl ester (2.0 g), and Et₃N (2 ml) were added at room temperature. The solution was stirred at room temperature under N₂ for four hours. The solvents were then evaporated under reduced pressure and the dark oily residue obtained was treated with water and extracted with CHCl₃. The CHCl₃ extract was washed with water, dried (Na₂SO₄) and evaporated to dryness. The reaction product (3.6 g) was purified by column chromatography (silica gel). The column was successively eluted with CHCl₃, and 10% MeOH/CHCl₃. The fractions containing the title compound were combined and purified again as above. The column was eluted first with CHCl₃, then with 2% MeOH/CHCl₃. The fractions containing the pure product were combined and evaporated in vacuo to provide the title compound.

196 EXAMPLE 54

197 (.+-.)-6-(CYSTEINYL POTASSIUM SALT)-7-EICOSYNE

198 0.64 g of compound from example 52 was stirred at room temperature under N.sub.2 with 60 ml of 0.13 M K.sub.2 CO.sub.3 in MeOH:H.sub.2 O (3:1) for 16 hours. Aqueous KOH (0.35 g/ml water) was added and the reaction stirred for 20 hours at room temperature. The solvents were evaporated under high vacuum. The solid residue was treated with water (25 ml) and the pH of the solution adjusted to 5.2. The mixture was taken in CHCl.sub.3 and the aqueous layer was separated. The organic layer was washed with water and dried over Na.sub.2 SO.sub.4. Evaporation of the solvent gave the title compound.

199 EXAMPLE 55

200 (.+-.)-6-(CYSTEINYL POTASSIUM SALT)-7-POTASSIUM LICOSYNATE

201 0.4818 g of product from example 53 was treated with 20 ml MeOH:H.sub.2 O (3:1) and cooled in ice bath under N.sub.2. 0.5 g of KOH in 3 ml of water was then added dropwise. The solution was let warm up to room temperature and stirred for a total of four hours. Aqueous KOH (0.25 g/ml) was added and after another hour, the solvents were evaporated under reduced pressure. The residue was dissolved in water (10 ml) and applied to an XAD-4 column (145 g). The column was successively eluted with water (10.times.20 ml), 30% MeOH/H.sub.2 O (6.times.20 ml), 50% MeOH/H.sub.2 O (5.times.20 ml) and MeOH (11.times.20 ml). The methanolic fractions gave 0.28 g of the title compound.

202 EXAMPLE 56

203 (.+-.)-6-(N-TRIFLUOROACETYL CYSTEINYL)-7-EICOSYNOIC ACID

204 0.4 g of compound prepared according to example 53 was stirred at room temperature under N.sub.2 in 57 ml of 0.13 M K.sub.2 CO.sub.3 in MeOH:H.sub.2 O (3:1) for five hours. The solvents were evaporated under high vacuum and the residue was purified using 250 g XAD-4 resin column in water. The column was eluted with water to pH=7, then with 250 ml of 30% MeOH/H.sub.2 O, 500 ml of 50% MeOH/H.sub.2 O, and 100% MeOH. The product (0.16 g) was further purified by preparative thin layer chromatography on SiO.sub.2 (40% MeOH/CHCl.sub.3). Yield: 0.035 g.

205 EXAMPLE 57

206 (.+-.)-6-(N-TRIFLUOROACETYL CYSTEINYL METHYL ESTER) 7-METHYL EICOSYNATE

207 0.7 g of the product prepared according to example 53 was treated at 0.degree. C. in Et.sub.2 O with large excess of CH.sub.2 N.sub.2 in Et.sub.2 O. Solvent was evaporated under N.sub.2 at room temperature. The reaction mixture was purified by column chromatography (SiO.sub.2) (CHCl.sub.3). Yield: 0.22 g.

208 EXAMPLE 58

209 (.+-.)-6-(6-OXYHEXAN-1-TETRAHYDROPYRAN-2-YL-ETHER)-7EICOSYN-1-(TETRAHYDROPYRAN-2-YL)-ETHER

210 Part A

211 21 ml (2.85M in Et.sub.2 O) EtMgBr was added dropwise to a solution of 1-tetradecyne in 120 ml of dry Et.sub.2 O at room temperature. After the addition, the brown solution was stirred at room temperature for one hour, then cooled (dry ice-acetone bath). 10.0 g 6-tetrahydropyran-2-yl-hexanal in 50 ml of dry Et.sub.2 O was added in one portion. The mixture was let warm up to room to temperature and stirred for two hours. 3.5 g NH.sub.4 CL in 30 ml water was then added. The mixture was diluted with Et.sub.2 O (total volume=750 ml), washed with water, and dried over Na.sub.2 SO.sub.4. The reaction mixture resulting from the evaporation of the solvent (20 g) was filtered through silica gel (350 g) using CHCl.sub.3 as

eluent. The product obtained (3.6 g) was used as such for part B.

212 Part B

213 0.9 g NaH (50% oil dispersion) was washed with hexanes under N.sub.2, then 4 ml of dry THF was added. 2.66 g of the product from part A was added at room temperature, and the mixture refluxed under N.sub.2 for three hours. After cooling to room temperature, 3.0 g of 1-iodo-6-tetrahydropyran-2-yl-ether was added and the mixture refluxed overnight under N.sub.2. The mixture was then cooled in ice bath and treated with water. The solution was taken in CH.sub.2 Cl.sub.2 (300 ml), washed with water to pH=7 and dried over Na.sub.2 SO.sub.4. The reaction product was purified by column chromatography (silica gel) (5% EtOAc/Hexanes). Yield: 1.0 g.

214 EXAMPLE 59

215 (.+-.)-6-(6-OXYHEXANOL)-7-EICOSYN-1-OL

216 1.0 gr (.+-.)-6-(6-oxyhexan-1-tetrahydropyran-2-yl-ether)-7-eicosyn-1-(tetrahydro pyran-2-yl)-ether was stirred at room temperature for seven hours with 15 ml methanol containing 50 mg of p-toluenesulfonic acid. The solution was kept overnight in the refrigerator, then treated with 3 ml MeOH:aq. NH.sub.3 (8:2). After evaporation of the solvents, the resulting oil was taken in CH.sub.2 Cl.sub.2 washed with water (3.times.50 ml), and dried over Na.sub.2 SO.sub.4. Yield: 0.65 g.

217 EXAMPLE 60

218 (.+-.)-6-(6-OXYHEXANOIC ACID METHYL ESTER)-7-EICOSYN-1-OIC ACID METHYL ESTER

219 The product from example 59 was oxidized and methylated using the same procedure as described in example 11. The reaction mixture was purified by column chromatography on silica gel (5% EtOAc/Hexanes).

220 EXAMPLE 61

221 (.+-.)-6-(6-OXYHEXANOIC ACID)-7-EICOSYN-1-OIC ACID

222 The product from example 60 (0.2 g) was hydrolysed using the same procedure as described in example 13. Yield: 0.195 g.

223 EXAMPLE 62

224 (-)-METHYL(5R,6S)-5-HYDROXY-6-{(2R)-2-(TRIFLUOROACETYLAMINO)-2-(METHOXYCARB ONYL)-ETHYLTHIO}-7-EICOSYNOATE AND

225 (+)-METHYL(5S,6R)-5-HYDROXY-6-{(2R)-2-(TRIFLUOROACETYLAMINO)-2-(METHOXYCARB ONYL)-ETHYLTHIO}-7-EICOSYNOATE

226 A solution of methyl-trans-5,6-epoxy-7-eicosynoate (0.3762 g) (preparative example X) in methanol (0.1 ml) containing Et.sub.3 N (0.8 ml) was treated with cysteine methylester N-trifluoroacetate (0.516 g). After 2 hours solvents were evaporated in vacuo and the residue distributed between water and CH.sub.2 Cl.sub.2. The organic phase was then separated and the aqueous phase extracted three times with CH.sub.2 Cl.sub.2. Combined CH.sub.2 Cl.sub.2 extracts were washed once with water, dried (Na.sub.2 SO.sub.2) and evaporated to dryness in vacuo to provide a thick yellow oil (1.0097 g). The reaction was repeated exactly as above using 1.22 g. trans-epoxide to provide another batch of the product (3.228g). The two products were combined and chromatographed on TLC grade silica gel using 20-30ethylacetate in .eta.-Hexane as eluent:

227 A. Less polar isomer 0.94 g, {.alpha.}.sub.d.sup.26 -10.9.degree. (CHCl.sub.3)

228 B. More polar isomer 0.66 g, {.alpha.}.sub.D.sup.26 +22.degree. (CHCl.sub.3)

229 Both isomers were obtained as waxy solids.

230 EXAMPLE 63

231 (-) - (5R,6S) -5-HYDROXY-6-{ (2R) -2-AMINO-2-CARBOXYETHYLTHIO} -7-EICOSYNOIC ACID
DIPOTASSIUM SALT

232 The less polar dimethylester from example 62 (0.4 g) was stirred with 90 ml 0.13M K.sub.2 CO.sub.3 in MeOH: water (3:1) at room temperature in N.sub.2 atmosphere. After 36 hours solvents were removed in vacuo (bath temp. 40.degree. C.) and the residue obtained subjected to purification on a XAD-4 (160 g) column:

233 Fractions: water (800 ml)-discarded 1-5 MeOH 0.2783 g amorphous solid (400) each
{.alpha.}.sub.D.sup.26-24.6 .degree. (MeOH)

234 EXAMPLE 64

235 (.+-.) - (5S,6R) -5-HYDROXY-6-{ (2R) -2-AMINO-2-CARBOXYETHYLTHIO} -7-EICOSYNOIC ACID
DIPOTASSIUM SALT

236 The more polar dimethylester (0.3 g) was stirred with 66 ml 0.13M K.sub.2 CO.sub.3 in MeOH:water (3.1) at room temperature in N.sub.2 atmosphere. After 36 hours the reaction was worked up as in example 63 and the product subjected to purification on a XAD-4 (120 g) column:

237 Fractions: Water (600 ml) 1-5 MeOH 0.2264 g (400 ml each) amorphous solid
{.alpha.}.sub.D.sup.26 +11.9.degree. (MeOH)

238 EXAMPLE 65

239 6-HYDROXY-6- (TETRADEC-1-YNLYDENE) -1,11-UNDECANE DICARBOXYLIC ACID (CRUDE)

240 A stirred solution of tetradecyne (58.2 g) in 55 ml dry tetrahydrofuran (THF) was treated (in argon atmosphere) dropwise with n-Buli (1.6 M in n-Hexane) until 85 ml had been added. A very heavy precipitation of Li-salt of tetradecyne took place causing difficulty in stirring the reaction mixture. After stirring the reaction mixture in ice bath for .about.-45 minutes, 6-keto undecanedicarboxylic acid (10.4 g) was added as a concentrated solution in dry THF (50 ml). The reaction mixture was gradually allowed to warm up to room temperature and stirred for a total 15 hours. The pasty reaction mixture was quenched with water and extracted with n-hexane to remove excess tetradecyne. The aqueous phase was adjusted to pH.about.2 with aqueous oxalic acid and extracted with CH.sub.2 Cl.sub.2. A crystalline solid not soluble in either phase later found to be unchanged ketodicarboxylic acid was removed by filtration. The CH.sub.2 Cl.sub.2 extract was dried (Na.sub.2 SO.sub.4) and evaporated to dryness to provide a crystalline solid. Yield: 6.36 g. This product was used as such in the next reaction.

241 EXAMPLE 66

242 1,11-UNDECANEDICARBOXYLIC ACID,6-HYDROXY-6 (TETRADEC-1-YLIDENE) DIMETHYLESTER

243 The crude diacid from example 65 (0.6 g) was treated with excess diazomethane as in example 4B and subjected to chromatography on six 1 mm thick silica gel plates (solvent system: 20% ethylacetate in n-hexane). The less polar major band was extracted with 20% MeOH/CHCl.sub.3 to provide a crystalline solid, m.p. 35.degree. C. Yield: 0.44 g.

244 EXAMPLE 67

245 6-HYDROXY-6- (TETRADEC-1-YNLYDENE) -1,11-UNDECANE DICARBOXYLIC ACID (PURE)

246 A solution of the pure diester from example 66 (0.22 g) in ethanol (5 ml) was treated with 10% aqueous NaOH (2.5 ml). The mixture was stirred for 36 hours at room temperature. Work-up of the reaction as in example 5 yielded a crystalline solid, m.p. 65.degree.-66.degree. C. Yield: 0.191 g.

247 EXAMPLE 68

248 6-(TETRADEC-1-YNLIDENE)-1,11-UNDEC-5Z-ENE DICARBOXYLIC ACID DIMETHYLESTER

249 A solution of the tert. alcohol-dimethylester from example 66 (1 g) in CH.sub.2 Cl.sub.2 (50 ml) was treated with cooling (bath temp 0.degree.-5.degree. C.) and good stirring with P.sub.2 O.sub.5 (0.8 g). After 1 hour the reaction was quenched with water. CH.sub.2 Cl.sub.2 phase was separated and the aqueous phase was extracted twice with more CH.sub.2 Cl.sub.2. The combined CH.sub.2 Cl.sub.2 extract was washed with aqueous NaHCO.sub.3, dried over Na.sub.2 SO.sub.4 and evaporated to dryness to provide the crude product (1.035 g) as a thick oil. It was purified by chromatography on coarse SiO.sub.2 (30 g) using 10% ethylacetate in n-hexane as eluent (50 ml fractions). The desired 5Z-olefin was obtained as the less polar component. Yield: 0.7564 g. The more polar fraction was a mixture of 5Z-(major) and 5E-(minor) olefins (0.2028 g).

250 EXAMPLE 69

251 6-(TETRADEC-1-YNLIDENE)-1,11-UNDEC-5Z-ENE DICARBOXYLIC ACID

252 A solution of the dimethylester from example 68 (0.2 g) in ethanol (5 ml) was treated with 10% aqueous NaOH (2.5 ml). The reaction mixture was stirred for 36 hours and worked up as in example 5 to provide the title compound as a crystalline solid, m.p. 47.degree.-48.degree. C. Yield: 0.196 g.

253 EXAMPLE 70

254 6-(TETRADEC-1-YNLIDENE)-1,11-UNDEC-5E-ENE DICARBOXYLIC ACID DIMETHYLESTER

255 Dehydration of 7 g. tert. alcohol-dimethylester (from example 66) was conducted as in example 68. The minor more polar 5E-olefin was isolated by repeated chromatography on TLC grade silica gel using 10% ethylacetate in-hexane as eluent. The partially purified 5E-olefin (0.149 g) was further purified by preparative thin layer chromatography.

256 EXAMPLE 71

257 6-(TETRADEC-1-YNLIDENE)-1,11-UNDEC-5E-ENE DICARBOXYLIC ACID

258 Hydrolysis of the 5E-olefin-dimethylester (0.16 g) as in example 69 gave the title compound as a crystalline solid. Yield: 0.15 g.

259 EXAMPLE 72

260 1,11-UNDECANEDICARBOXYLIC ACID, 6-FLUORO-6-(TETRA DEC-1-YNLIDENE)DIMETHYLESTER

261 A stirred solution of the 6-hydroxy-dimethylester (1 g; example 66) in CH.sub.2 Cl.sub.2 (5 ml) was cooled (ice bath) and treated with diethylaminosulfurtrifluoride (DAST) (0.7 ml; excess). After 30 minutes in the ice bath, the reaction was allowed to warm up to room temperature. The reaction mixture was stirred for a total of 1 1/2 hours followed by treatment with dilute NaHCO.sub.3 solution. CH.sub.2 Cl.sub.2 layer was separated and the aqueous phase extracted once more with CH.sub.2 Cl.sub.2. The combined organic extracts were washed once with water, dried (Na.sub.2 SO.sub.4) and evaporated to dryness to provide a gummy product. It was chromatographed on TLC grade SiO.sub.2 (50 g) using 10% ethylacetate in n-hexane as eluent (.about.5 ml fractions). The desired 6-fluoro-dimethylester was isolated from the more polar fractions 47-52 as a colorless oil. Yield: 0.4856 g.

262 EXAMPLE 73

263 6-FLUORO-6-(TETRADEC-1-YNYLIDENE)-1,11-UNDECANEDICARBOXYLIC ACID

264 A solution of the fluoro-diester from example 720 (0.22 g) in ethanol was

hydrolysed with 10% aqueous NaOH (3 ml) as in example 5. Work-up in the same manner provided the desired diacid as a crystalline solid, m.p. 98.degree.-100.degree. C. Yield: 0.2051g.

265 EXAMPLE 74

266 6-FLUORO-6-(TETRADECYL-1,11-UNDECANEDICARBOXYLIC ACID DIMETHYLESTER

267 A solution of the acetylenic alcohol (0.4 g); from example 73) in n-hexane (40 ml) was hydrogenated in the presence of 10% Pd/C (0.1 g). After 15 hours the catalyst was removed by filtration, washed with CH₂Cl₂ and the combined filtrates and washings were evaporated to dryness to provide a thick colorless oil. Yield: 0.4

268 EXAMPLE 75

269 6-(TETRADECANYL)-1,11-UNDECANEDICARBOXYLIC ACID DIMETHYLESTER

270 A solution of the unsaturated diester (0.3 g; example 68) in n-hexane (30 ml) was hydrogenated in the presence of 10% Pd/C (0.1 g) overnight. Catalyst was removed by filtration and washed with CH₂Cl₂. Evaporation of combined filtrates gave the title compound as a thick colorless oil. Yield: 0.3 g.

271 EXAMPLE 76

272 6-(TETRADECANYL)-1,11-UNDECANE DICARBOXYLIC ACID

273 A solution of the diester (0.2 g; from example 75) in ethanol (5 ml) was treated with 10% aqueous NaOH (2.5 ml) exactly as in example 5 to provide a crystalline solid, m.p. 48.degree.-50.degree. C.

274 EXAMPLE 77

275 6-HYDROXY-6-(TETRADECYL)-1,11-UNDECANEDICARBOXYLIC ACID

276 A solution of the saturated diester (0.23 g; example 74) in ethanol (8 ml) was treated with 10% aqueous NaOH (2.5 ml) as in the previous experiment. The product after trituration with n-hexane provided a crystalline solid, m.p. 79.degree.-80.degree. C. Yield: 0.1896 g.

277 EXAMPLE 78

278 6-(TETRADEC-1-YNLIDENE)-1,11-UNDECANEOLIOIC ACID

279 (The synthesis of the title compound is described in part E of this example)

280 Part A

281 To a solution of 6-(tetradec-1-ynlidene)-1,11undec-5Z-ene dicarboxylic acid dimethylester (1.0g.; example 68) was added (under N₂) dicobalt octacarbonyl (0.94 g.) in dry CH₂Cl₂ at room temperature. The reaction was stirred for 1 hr. followed by removal of CH₂Cl₂ under N₂ atmosphere.

282 Part B

283 A solution of the product from the above reaction (1.5 g.) in dry methanol (25 ml) was added to a slurry of potassium diazodicarboxylate (5.06 g.) in dry methanol (25 ml) in an atmosphere of N₂. The reaction mixture was cooled (ice bath) and a solution of glacial acetic acid (2.7 ml) in dry methanol (7.3 ml) was added dropwise. The mixture was stirred in ice bath for three hours. Four additions of potassium diazodicarboxylate (as a solid) (3.3 g.) along with glacial acetic acid (1.5 ml) in dry methanol (8.5 ml) were necessary at three hour intervals. After evaporation of methanol in vacuo the residue was dissolved in CHCl₃, washed with aqueous NaHCO₃, water and dried (Na₂SO₄) Evaporation of the solvent in vacuo left the crude product (1.07 g.).

284 PART C

285 A portion of the reaction product from above (0.722 g.) was dissolved in acetone (25 ml) and the solution cooled (ice bath). Ceric ammonium nitrate (3.3g.) was added in small portions over a period of 30 minutes with good stirring. The reaction mixture was stirred for an additional 15 minutes followed by addition of n-hexane (200 ml). the organic phase was washed with water, dried (Na.sub.2 SO.sub.4) and evaporated to dryness to provide the crude dimethylester of the title compound containing unchanged olefinic dimethylester.

286 Part D

287 The above mixture was treated with m-chloroperbenzoic acid as described in preparative example XII. A mixture of the epoxide derived from the unchanged olefinic dimethylester and unreacted dimethylester of the title compound was thus obtained. The two products were separated by chromatography on t.l.c. grade silica gel. The pure dimethylester of the title compound so obtained was treated as follows.

288 Part E

289 A portion (0.1g.) of 6-(tetradec-1-ynlidene 1,11-undecandecioic acid dimethylester (as obtained from Part D) was treated with 10% aqueous KOH as in example 13 to provide the title compound. Yield: 0.09 g.

290 EXAMPLE 79

291 HEPTANOIC ACID-6,6'-{PENTADECYN-1-YLIDENE
BIS(OXY)}-BIS-(2,2-DIMETHYL-1-OXOPROPOXYMETHYL) ESTER

292 To a stirred solution of heptanoic acid-6,6'-{2-pentadecyn-1-ylidene bis(oxy)}bis (0.5 g) in dry DMF (3 ml) was added dry Et.sub.3 N (0.77 ml). The solution was cooled in an ice bath and a solution of chloromethyl pivalate (0.34 ml) was added. The solution was allowed to warm to room temperature and stirred in an argon atmosphere for .about.15 hrs. The solvent was evaporated in vacuo, the residue treated with water (20 ml) and extracted several times with ethyl acetate. The combined extracts were washed with water, dried (Na.sub.2 SO.sub.4) and evaporated to dryness to provide a gummy product. The impure product was filtered through a column of SiO.sub.2 (30 g) using CHCl.sub.3 as eluent. Yield: 0.7 g.

293 PREPARATIVE EXAMPLE I

294 2-PENTADECYNAL DIETHYLACETAL

295 Tetradecyne (100 g), (EtO).sub.3 CH (200 ml) and ZnI.sub.2 (15 g) were heated together (bath temperature 170.degree.-175.degree.) with distillative removal of ethanol (.about.90 minutes). The reaction mixture was evaporated in vacuo (bath temperature 80.degree.) to remove excess (EtO).sub.3 CH. The residue was distributed between CH.sub.2 Cl.sub.2 and water. The CH.sub.2 Cl.sub.2 phase was separated, washed with aqueous NaHCO.sub.3, dried (Na.sub.2 SO.sub.4) and evaporated in vacuo to provide a light brown oil. Yield: 135.4 g. This product was shown to be virtually pure by TLC and PMR and it was used as such in subsequent reactions.

296 PREPARATIVE EXAMPLE II

297 2-PENTADECYNAL

298 A mixture of 2-pentadecynal diethyl acetal (4g) and 10% aqueous H.sub.2 SO.sub.4 (60 ml) was refluxed with efficient stirring, for one hour. An additional 40 ml dilute H.sub.2 SO.sub.4 was added at this stage and the mixture heated for another two hours. After cooling, the reaction mixture was extracted with CH.sub.2 Cl.sub.2, the extract dried (Na.sub.2 SO.sub.4) and evaporated in vacuo to provide a yellow oil. Yield: 2.9 g.

299 PREPARATIVE EXAMPLE III

300 5-FORMYL-3E-ENE-2-PENTYNAL DIETHYL ACETAL

301 A stirred solution of diformyl acetylene monodiethylacetal (2.28 g) was treated in small portions with Ph.sub.3 P=CH.CHO (4.47 g). After stirring for 15 hours the solvent was evaporated in vacuo and the dark residue subjected to chromatography on coarse SiO.sub.2 (100 g) using 5% acetone/n-hexane as eluent. Fractions (100 ml) were collected and the title compound was obtained pure from fraction no. 6. Yield: 2.01 g.

302 PREPARATIVE EXAMPLE IV 4E,6Z,9Z-PENTADECATRIENE-2-YNE ALDEHYDE DIETHYL ACETAL

303 A solution of 3-(Z)-nonene-triphenylphosphonium salt in 20-23 ml of dry THF was treated with 1.6M BuLi (6.79 ml) and stirred at room temperature for 1 hour. The aldehyde (1.68 g, example III) in 3 ml THF was added and allowed to stir for another 3 hours. The reaction mixture was diluted with EtOAc and washed with dilute NaHSO.sub.3 solution, brine and dried (Na.sub.2 SO.sub.4). Evaporation of the solvent followed by chromatography on SiO.sub.2 (eluent 10% Et.sub.2 O in n-hexane) gave the pure product (1.17 g) as a yellow oil.

304 PREPARATIVE EXAMPLE V

305 6(+.-.)-HYDROXY-7-EICOSYN-METHYLCARBOXYLATE

306 A cooled solution (ice bath) of the 6-ketone (29.86 g) in methanol (475 ml) and water (10 ml) was treated with NaBH.sub.4 (1.27 g) in small portions. After 30 minutes the reaction was diluted with water (50 ml), methanol evaporated in vacuo and the residue distributed between water (50 ml) and CH.sub.2 Cl.sub.2 (100 ml). CH.sub.2 Cl.sub.2 phase was extracted twice with CH.sub.2 Cl.sub.2. The combined CH.sub.2 Cl.sub.2 extracts were dried (Na.sub.2 SO.sub.4) and evaporated to dryness to provide the almost pure alcohol as a thick oil (30.23 g). It was further purified on coarse silica gel (300 g) using 5% ethyl acetate/n-hexane as eluent. Fractions 7-18 (250 ml each) gave the pure alcohol. Yield: 21.79 g.

307 PREPARATIVE EXAMPLE VI

308 (+) 6(R)-HYDROXY-7-EICOSYN-METHYLCARBOXYLATE

309 A solution of (+) .alpha.-pinene (1.04 ml; { .alpha. }.sub.D.sup.26 47.7.degree.) and 9-borabicyclononane (12 ml of 0.5M THF solution; 0.006 mol) was refluxed for 21/2 hours and cooled to room temperature. With ice bath cooling 6-oxo-eicosa-7-yne-methylcarboxylate (1 g; 0.003 mol) was now added. The mixture was now stirred under argon at room temperature for 3 days. Acetaldehyde (21 ml) was injected into the solution which was then stirred for 15 minutes. The THF and (+) .alpha.-pinene were removed in vacuo at 40.degree. (bath temperature). The remaining yellow product was treated with diethylether (5 ml) to dissolve, followed by addition of ethanolamine (0.38 g; 0.006 mol). After stirring at ice bath temperature for 15 minutes the, white precipitate formed was removed by filtration and washed with cold diethylether. The combined filtrate was washed with saturated NaCl, dried (Na.sub.2 SO.sub.4) and evaporated to dryness to provide a thick oil. It was chromatographed on TLC grade SiO.sub.2 (100 g) using 10% ethyl acetate in n-hexane as eluent. Fractions 103-135 (.about.5 ml each) gave pure 6R-alcohol. Yield: 0.6268 g. Note: The 6(S)-alcohol of opposite configuration was obtained by substituting (+) .alpha.-pinene with (-) .alpha.-pinene in the above reaction.

310 PREPARATIVE EXAMPLE VII 2-PENTADECYNE 1-OL

311 A stirred solution of the aldehyde from preparative example II (16.56 g) in methanol (160 ml) and water (16 ml) was cooled (ice bath) and treated with NaBH.sub.4 (1.25 g) in small portions. After .about.10 minutes a crystalline precipitate separated. Stirring was continued for 30 minutes. The solvents were evaporated in vacuo and the residue was distributed between CH.sub.2 Cl.sub.2

(.about.100 ml) and water (.about.50 ml). CH.sub.2 Cl.sub.2 phase was separated and the aqueous phase extracted twice with CH.sub.2 Cl.sub.2. The combined CH.sub.2 Cl.sub.2 extracts were washed once with water, dried (Na.sub.2 SO.sub.4) and evaporated to dryness to provide a crystalline solid, m.p. 36-37.degree. C. Yield: 17.8 g.

312 PREPARATIVE EXAMPLE VIII 1-BROMO-2-PENTADECYNE

313 A stirred solution of the alcohol (17 g; preparative example VII) in CH.sub.2 Cl.sub.2 (500 ml) was treated with CBr.sub.4 (30.19 g). After all CBr.sub.4 had dissolved, the solution was cooled (ice bath) and treated with Ph.sub.3 P (25.87 g). The reaction was worked up after 1 hour as follows: CH.sub.2 Cl.sub.2 was evaporated in vacuo and the gummy residue treated with n-hexane. A precipitate of Ph.sub.3 P=O so obtained was removed by filtration and washed with n-hexane. The combined filtrate and washings were evaporated to dryness in vacuo and passed through a column of coarse SiO.sub.2 (200 g) using n-hexane (.about.2L) as eluent. Evaporation of the n-hexane eluate in vacuo (temp. 60.degree.-90.degree.) provided the bromide as a colorless oil. Yield: 19.9 g.

314 PREPARATIVE EXAMPLE IX

315 2-PENTADECYNE-1-TETRAMETHYLENE SULFONIUM BROMIDE

316 To a solution of the bromide (18.9 g.; preparative example VIII) in 150 ml methanol:water (9:1) was added tetrahydrothiophene (7.56 g). The reaction mixture was efficiently stirred for 2 days. After washing once with n-hexane, the MeOH:water phase was evaporated to dryness and the residue dissolved in CH.sub.2 Cl.sub.2. The methylene chloride solution was concentrated to .about.10 ml and treated with n-hexane until separation of colorless crystals took place. The crystals were collected by filtration. Yield: 13.6 g, m.p. 76.degree.-79.degree. C.

317 PREPARATIVE EXAMPLE X TRANS-5,6-EPOXY-7-EICOSYNOIC ACID METHYL ESTER/CIS-5,6-EPOXY-7-EICOSYNOIC ACID METHYL ESTER

318 A stirred and cooled solution (bath temperature -25.degree.) of the tetramethylene sulfonium bromide (3 g; preparative example IX) methyl 4-formylbutyrate (1.04 g) containing benzyltriethylammonium chloride (0.054 g) in CH.sub.2 Cl.sub.2 (15 ml) was treated with 10M NaOH solution (8.06 ml) in one portion. The mixture was efficiently stirred for 1 min. and then rapidly cooled to =70.degree. (bath temp.). CH.sub.2 Cl.sub.2 layer was decanted out with a pipette. The frozen aqueous phase was washed 3-4 times with CH.sub.2 Cl.sub.2, the combined CH.sub.2 Cl.sub.2 extract and washings were washed with water, dried (Na.sub.2 SO.sub.4) and evaporated to dryness to provide a turbid oil. The products from four such reactions were combined to yield 14.2 g total crude product which was chromatographed on TLC grade SiO.sub.2. The column was eluted with 50% n-hexane/CHCl.sub.3 containing 2 ml/1L triethylamine) and .about.6 ml fractions were collected:

319 Fractions 102-132 Pure trans-epoxide

320 Fractions 191-205 Pure cis-epoxide

321 PREPARATIVE EXAMPLE XI (.+-.) METHYL-6-BROMO-7-YNE-EICOSANOATE

322 This compound was prepared by reaction of 6(.+-.)-hydroxy-7-eicosyn-methylcarboxylate (preparative example V) with CBr.sub.4 /Ph.sub.3 P reagent in exactly the same manner as described in preparative example VIII. Note: By use of the corresponding 6-R, and 6-S alcohols (preparative example VI) the optically active (+) and (-) 6-bromo-7-yne-eicosanoates were also obtained.

323 PREPARATIVE EXAMPLE XII

324 6-(TETRADIC-1-YNLIDENE)-5,6-EPOXY-1,11-UNDECANEDIOIC ACID DIMETHYL ESTER

325 0.19 g. of the product from example 70 was cooled in ice bath and meta-chloroperbenzoic acid (0.07 g) was added. Additional 0.1 g peracid was added in two portions after two and three hours period. Two hours later, the reaction mixture was diluted with CH₂Cl₂ (180 ml), washed with aqueous NaHSO₃, aqueous Na₂CO₃ (3.times.50 ml), then with water and dried over Na₂SO₄. The reaction mixture was purified by column chromatography on silica gel (CHCl₃). The fractions containing the title compound were further purified by preparative thin layer chromatography on silica gel (20% EtOAc/hexanes). Yield: 0.139 g.

326 PREPARATIVE EXAMPLE XIII

327 (.+.)-DIPOTASSIUM-{6-(TETRADEC-1-YNE YLIDENE)-5,6-EPOXY}-1,11-UNDECANEDIOATE

328 0.37 g. 6-(tetradec-1-ynlidene)-5,6-epoxy-1,11-undecanedioic acid dimethyl ester was stirred at room temperature with 5 ml of absolute EtOH and 1.84 ml of 10% aqueous KOH for 24 hours. The solvents were then evaporated and the mixture was desalted on a XAD-4 resin (35 g) column. The column was eluted first with water to pH=7, then with 50% H₂O/MeOH to provide in methanolic fractions the title compound.

CLAIMS:

We claim:

1. A process for treating a human being for hyperproliferative skin disease comprising the topical administration of an effective amount of a compound having the structural formula I, II or III: ##STR17## wherein T is straight or branched chain alkyl having from 7 to 15 carbon atoms which may optionally contain from 1 to 3 non-cumulative double or triple bonds;

U is --CH₂CH₂--, --CH.dbd.CH-- or --C.tbd.C--;

V is a straight or branched chain alkylene having from 1 to 4 carbon atoms or is a direct bond;

W and W¹ may be the same or different and are O or S(O)_m wherein m is 0, 1 or 2;

X and X¹ may be the same or different and are straight or branched chain alkylene having from 2 to 12 carbon atoms which may optionally contain from 1 to 3 non-cumulative double or triple bonds and which may optionally be substituted with --NHR^a {wherein R^a is hydrogen, alkyl having from 1 to 6 carbon atoms, COCF₃, CO(CH₂)₂CH(NH₂)CO₂H, or SO₂R^b (wherein R^b is alkyl having from 1 to 6 carbon atoms or CF₃)};

R¹ is hydrogen or straight or branched chain alkyl having from 1 to 6 carbon atoms;

R² and R³ may be the same or different and are CH₂OR^c {wherein R^c is hydrogen, carboxylic acyl having from 1 to 6 carbon atoms, tetrahydropyran-2-yl or COCH₂CH₂CO₂H}, CHO, 2-tetrazolyl, COR^d {wherein R^d is hydroxy, alkoxy having from 1 to 6 carbon atoms, OCH₂OC(O)C(CH₃)₃, NHR^e (wherein R^e is hydrogen, alkyl having from 1 to 6 carbon atoms or CH₂CO₂H)} or SO₃H, with the proviso that at least one of R² and R³ is 2-tetrazolyl or carboxyl; ##STR18## wherein T, U, V, W, X, R² and R³ are defined above;

Y is straight or branched chain alkylene having from 1 to 12 carbon atoms which may optionally be substituted with the group OR^c {wherein R^c is as defined above} and may optionally contain from 1 to 3 non-cumulative double or triple bonds; or ##STR19## wherein T, U, V, R² and R³ are defined above;

Z and Z¹ may be the same or different and are straight or branched chain

alkylene having from 1 to 12 carbon atoms which may optionally contain from 1 to 3 non-cumulative double or triple bonds;

R^{sup.4} is hydrogen, hydroxyl, or is combined with Z to form a double bond as indicated by the dashed line "a" or a cyclopropyl ring as indicated by the dashed lines "b", or 1-methane,1,1-{(2-pentadecynylidene) bis(oxy)} bis carboxylic acid.

2. The process defined in claim 1 wherein the compounds have structural formula I.

3. The process defined in claim 2 wherein:

T is straight chain alkyl having from 7 to 15 carbon atoms;

U is --C.tbd.C--;

V is a direct bond;

W and W^{sup.1} are O or S;

X and X^{sup.1} are straight or branched chain alkyl having from 2 to 8 carbon atoms;

R^{sup.1} is hydrogen; and

R^{sup.2} and R^{sup.3} are COOH.

4. The process defined in claim 1 wherein the compounds have structural formula II.

5. The process defined in claim 4 wherein:

T is straight chain alkyl having from 7-15 carbon atoms;

U is --C.tbd.C--;

V is a direct bond;

W is O or S;

X and Y are straight or branched chain alkyl having from 2 to 6 carbon atoms; and

R^{sup.2} and R^{sup.3} are COOH.

6. The process defined in claim 1 wherein the compounds have structural formula III.

7. The process defined in claim 6 wherein:

T is straight chain alkyl having from 7-15 carbon atoms;

U is --C.tbd.C--;

V is a direct bond;

Z and Z^{sup.1} are straight or branched chain alkyl having from 2 to 6 carbon atoms;

R^{sup.2} and R^{sup.3} are COOH; and

R^{sup.4} is hydrogen, hydroxyl or is combined with Z to form a double bond.

8. A process defined in claim 1, wherein the compound has structural formula I, II or III wherein the substituents T-U-V- are combined to form the n-1-teradecyn-1-yl

group, i.e. n--C.sub.12 H.sub.25 C.tbd.C--.

9. A process defined in claim 8 wherein the substituents R.sup.2 and R.sup.3 are COOH.

10. The process defined in claim 1 wherein the disease is psoriasis, lichenified eczema or seborrhoeic dermatitis.

11. The process defined in claim 1 wherein the disease is psoriasis.

12. A process defined in claim 1 wherein the compound has the following name:

1-propane, 3,3'-{(2-pentadecynylidene)bis(oxy)}bis-carboxylic acid;

1-methane, 1,1'-{(2-pentadecynylidene)bis(oxy)}bis-carboxylic acid;

1-pentane, 5,5'-{(2-pentadecynylidene)bis(oxy)}bis-carboxylic acid;

(.+-.)-1-butane, 3,3'-{(2-pentadecynylidene)bis(oxy)}bis-carboxylic acid;

1-butane, 4,4'-{(2-pentadecynylidene)bis(oxy)}bis-carboxylic acid;

(.+-.)-1-hexane, 5,5'-{(2-pentadecynylidene)bis(oxy)}bis-carboxylic acid;

(.+-.)-6-(4-oxybutan-1-ol)-5-oxaeicos-7-yn-1-oic acid;

1-propane, 3,3'-{(2-pentadecynylidene)bis(thio)}bis-carboxylic acid;

1-butane, 4,4'-{(2-pentadecynylidene)bis(thio)}bis-carboxylic acid;

(.+-.)-1-pentane, 4,4'-{(2-pentadecynylidene)bis(oxy)}bis-carboxylic acid;

(.+-.)-6-(carboxyethylthio)-7-yne eicosanoic acid;

(.+-.)-6-(carboxypropylthio)-7-yne eicosanoic acid;

(+) and (-)-6-(carboxypentylthio)-7-yne eicosanoic acid;

(.+-.)-6-(carboxypentyloxo)-7-yne eicosanoic acid;

6-hydroxy-6-(tetradec-1-ynylidene)-1,11-undecanedi-carboxylic acid;

6-(tetradec-1-ynylidene)-1,11-undecanedcarboxylic acid;

6-(tetradec-1-ynylidene)-1,11-undec-5-(E) and (Z) ene dicarboxylic acids;

(.+-.)-1-butane, 3,3'-{(2-pentadecynylidene)bis(thio)}bis-carboxylic acid; or

(.+-.)-1-pentane, 4,4'-{(2-pentadecynylidene)bis(thio)}bis-carboxylic acid.

13. A method of treating hyperproliferative skin disease in a mammal comprising topical administration of an effective amount of 1-methane, 1,1'-{(2-pentadecynyliden) bis(oxy)}bis carboxylic acid.